



A Toxidromic Approach for Chemical Medical Countermeasure Development

The Development of Ferrets as an Animal Model for Carfentanil Toxicity

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Carfentanil is a synthetic opioid that is 10,000 times more potent than morphine and 100 times more potent than fentanyl. It produces analgesia, incapacitation, respiratory depression, and death at various doses, but its toxicity has been elaborated only to a limited extent using laboratory animal models. As such, an animal model of carfentanil toxicity is needed for future medical countermeasure development. However, several potential animal models have disadvantages: swine poorly model the human behavioral response to opioids (i.e., agitation instead of sedation), non-human primates are costly to acquire and maintain, and rats have an opioid resistance that requires significantly higher doses to achieve the same toxicity as other mammals, such as humans. Ferrets have none of these disadvantages and the pulmonary structure and function of ferrets resembles that of humans, making the ferret an excellent animal model for investigating inhaled toxicants. To develop ferrets as a model of opioid toxicity, a series of experiments were conducted. First, the median lethal dose of carfentanil was determined with water-regulated and unregulated male ferrets to carfentanil via subcutaneous injection, which provides a controlled method of exposure that is also safe and easily achieved. Initial toxic signs were lethargy and ataxia, which progressed to fasciculation and unconsciousness at moderate doses. At higher doses, respiratory distress and death were comorbid with occasional convulsions. The median lethal dose was estimated to be 27.77 $\mu\text{g}/\text{kg}$, and water regulation status did not alter carfentanil toxicity. Second, carfentanil was used a challenge after ferrets were behaviorally trained in an operant-behavior assessment where a lever was pressed for access to water. A wide range of doses produced behavioral deficits and this behavioral assessment was sensitive enough to detect behavioral deficits with doses as low as 1/10th of the median dose (2.37 $\mu\text{g}/\text{kg}$), which otherwise produced only transient and mild overt toxic signs (i.e., ataxia, lethargy). Third, a shock-avoidance assessment where ferrets worked to terminate or prevent a shock instead of access to water. This addressed potential nausea or consummatory concerns while also providing data on a secondary behavioral assessment. Again, the behavioral assessment showed deficits with very low doses (3.16 $\mu\text{g}/\text{kg}$). These data help to elaborate carfentanil toxicity in an animal model that offers advantages for studies of inhaled toxicants, and provide a relevant foundation for ongoing and planned studies of inhalation, subcutaneous, and intravenous carfentanil exposure and medical treatment of opioid overdose.